REMARKS

The Examiner is thanked for the due consideration given the application. A verified translation of the priority document is attached to this paper.

Claims 12-15 and 17-29 are pending in the application. Claims 16 and 30 have been canceled by this amendment. Claim 28 has been withdrawn. Support for the amendments to claims 12 and 13 can be found in paragraph 0044 of the U.S. Publication of the application. The amendments to claims 14 and 29 find support in paragraph 0032 of the U.S. Publication of the application. Claims 15, 17-19, 22-24, 25 and 29 have been amended to improve their language in a non-narrowing fashion.

No new matter is believed to be added to the application by this amendment.

Rejection Under 35 USC §112, Second Paragraph

Claims 12-27, 29 and 30 have been rejected under 35 USC §112, second paragraph as being indefinite. This rejection is respectfully traversed.

The comments in the Official Action have been considered, and the claims have been appropriately amended. However, it is noted that the term "blood" in claim 24 finds antecedent basis in line 4 of claim 12.

The claims are thus clear, definite and have full antecedent basis.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejection Under 35 USC §112, First Paragraph

Claims 12, 13, 17, 18 and 20-27 have been rejected under 35 USC §112, first paragraph as not being enabled. This rejection is respectfully traversed.

The Official Action asserts that the specification is enabling for processing fresh plasma but does not reasonably provide enablement for processing frozen plasma.

Although the examples in the specification use only fresh plasma, and paragraph 0032 of the U.S. Publication sets forth that fresh plasma is preferable, the bonding of proteins, lipids and so on during a long storage causes a reduction in permeability, and the freeze itself does not cause this reduction.

Thus, a person skilled in the art would be able to practice the present invention using frozen plasma without undue experimentation.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejection Over BURNOUF et al.

Claims 12-27, 29 and 30 have been rejected under 35 USC §102(a) as being anticipated by BURNOUF et al. (*Vox Sanguinis* 84: 111-119 (2003)). This rejection is respectfully traversed.

The present invention claims priority of Japanese Application 2002-301433, filed on October 16, 2002, which is before the 2003 publication date of BURNOUF et al.

In order to perfect priority, a verified translation of the priority document is attached to this paper, thus removing BURNOUF et al. as prior art to the present invention.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejections Based On JP 64-0501075

Claims 12-16, 18-26, 29, and 30 have been rejected under 35 U.S.C. 103(a) as being unpatentable over JP 64-051075. Claim 27 has been rejected under 35 U.S.C. 103(a) as being unpatentable over JP 64-051075 in view of JP 3-146067. These rejections are respectfully traversed.

The present invention pertains to a method for producing a plasma product that includes separating plasma from whole blood, reducing leukocytes in the plasma, and filtering the plasma with a virus removing membrane.

JP 64-051075 discloses a method of treating blood that includes filtering the blood through a leukocyte filter, separating the plasma, and passing the plasma through a virus removing membrane. The invention described in JP 64-051075 relates to a device for removing viruses from blood fluid, particularly, from plasma.

The order of the steps is not the same as in the present invention. That is, leukocytes in the blood including plasma/serum is reduced prior to or after separation of red cells and platelets (i.e., prior to or after obtaining only plasma). Nonetheless, the Official Action asserts that changing the order is obvious lacking a showing of unexpected results.

As asserted by the Official Action, JP 64-051075 describes a method of treating blood that includes filtering the blood through a leukocyte filter, separating the plasma, and passing the plasma through a virus removing membrane (FIG. 1). The plasma is separated after reducing leukocytes from the blood. Although it is desirable to remove viruses incorporated in the leukocytes together with the leukocytes, the process has been designed in order to remove viruses contained in both plasma and leukocytes because free viruses are also included in plasma.

On the other hand, in the present invention, after separating plasma from the whole blood and reducing leukocytes in the plasma in step (a), the plasma is filtered using a virus removal filter in the filtration step (b). The order in step (a) of the present invention differs from the order in the invention of the reference.

Specifically, in step (a) of the present invention, it is important to separate plasma first and then reduce leukocytes. The order of leukocyte removal followed by plasma separation

described in JP 64-051075 cannot be employed in the present invention.

If the order of leukocyte removal before plasma separation as practiced in JP 64-051075, the filter pressure increases during the virus filtering step (b) and interferes with the virus filtering operation. This is clearly shown in Comparative Example 2 of the present invention, in which the virus filtering operation was terminated due to the inappropriate order of the steps (i) whole blood collection, (ii) leukocyte removal, and (iii) plasma separation. This operational problem was solved in the method of the present invention as shown in Example 1.

JP 64-051075 neither describes nor suggests the order of plasma separation followed by leukocyte removal, and the resulting outstanding effect of separation of the present invention.

Therefore, the present invention is not *prima facie* unpatentable over JP 64-051075 because the specification of the present invention demonstrates the criticality of the order of steps.

JP 3-146067 fails to address the deficiencies of JP 64-051075 discussed above.

One of ordinary skill and creativity would thus fail to produce a claimed embodiment of the present invention from a knowledge of JP 64-051075 or a combination or JP 64-051075 with

JP 3-146067. A *prima facie* case of unpatentability has thus not been made.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Rejections Based On HERMAN et al.

Claims 12-16, 18-26, 29 and 30 have been rejected under 35 USC §103(a) as being unpatentable over HERMAN et al. (U.S. Patent 6,190,855) in view of LEE et al. (U.S. Patent 6,861,001) and WO 01/14047. Claim 27 has been rejected under 35 USC §103(a) as being unpatentable over HERMAN et al. in view of LEE et al. and WO 01/14047, and further in view of JP 3-146067. These rejections are respectfully traversed.

HERMAN et al. pertain to a method of removing infectious agents from a blood component in two steps, a first step of causing serum to flow through a filter (particularly a leukocyte removing filter) to remove cellular matter which may contain viruses, and a second step of removing non-entrained viruses by a chemical agent in a photoactive reaction.

In HERMAN et al., plasma is treated to remove contaminants such as leukocytes and visitor virus factors (which may be included in plasma in a free form or may be entrapped in leukocyte cells in plasma). Specifically, the method of HERMAN et al. removes viruses entrapped in leukocyte cells by removing the leukocytes from plasma and, at the same time, inactivates

free viruses not entrapped in leukocyte cells by activating a photoactive compound added to the plasma.

In contrast, the present invention filters the plasma with a virus removal filter during the filtration step (b) after separating plasma from the whole blood and reducing leukocytes in the plasma in step (a). The present invention can thus superficially be analogized to the invention of HERMAN et al. insofar as the method has a step of reducing leukocytes from the plasma, but differs from the invention of HERMAN et al. in that the method of the present invention does not have to add a special reagent, i.e., a photoactive compound.

The reagent addition method of HERMAN et al. not only requires a complicated process of removing the added reagent, but also has a problem caused by the reagent remaining in the treated plasma preparation (see page 1 of the specification of the present invention in the Background Art section).

In the present invention, such a reagent is not added, but a filtration step using a virus-removing membrane is provided as step (b) after the leukocyte-reducing step. As a result, not only is it unnecessary to add a special reagent, but also a step of removing the reagent after treatment need not be provided. In addition, dead cells of free viruses can also be removed from plasma. Therefore, there is no risk of a large amount of dead cells of viruses remaining in the plasma after deactivation, as in the case of the invention of HERMAN et al. The method of the

present invention is thus more preferable from the viewpoint of safety.

HERMAN et al. neither describe nor suggest the filtration step using the virus removing filter of the present invention, and the resulting outstanding effect of the filtration step.

On the other hand, LEE et al. relate to a method of using a membrane to remove or entrap viruses from plasma and commercially-available biological fluids, or to purify the plasma and commercially-available biological fluids. More specifically, LEE et al. remove viruses by filtering a liquid using a membrane grafted with a positively charged polymer which interacts with viruses. As indicated by the Official Action, liquids containing cells such as human blood or other large particles require pre-treatment to separate the cells from the liquid prior to passing the liquid through the membrane (column 6, lines 27-30).

However, LEE et al. specifically describe neither "a method for producing a human or animal plasma product" nor "a step of filtering the plasma through a virus removing membrane" after "reducing leukocytes in the plasma" separated from the whole blood". See claim 12 of the present invention.

WO 01/14047 relates to a filter membrane used to effectively remove pathogens such as viruses from solutions of drugs or physiologically active substances used as the raw materials. More specifically, WO 01/14047 relates to a membrane

of which various properties, permeability of an index virus, and protein permeability are respectively defined in specific ranges.

However, WO 01/14047 only focuses on removing viruses, and fails to disclose or suggest the necessity of reducing leukocytes before filtering using the virus-removing membrane. As indicated in Comparative Example 1 of the present invention, filtration using a virus-removing membrane without reducing leukocytes involves a pressure increase which may result in interruption of filtration. The method of WO 01/14047 thus corresponds to the method of Comparative Example 1.

LEE et al. and WO 01/14047 thus neither describe nor suggest the constitution and effect of the present invention.

Also, the references cannot be combined.

First, in the process of HERMAN et al., leukocyte removal and virus removal (inactivation with light) are employed in combination in order to remove viruses entrapped in leukocytes and free viruses. Since viruses entrapped in leukocytes cannot be inactivated by a photoreaction and free viruses cannot be removed by leukocyte removal, removal in two steps is essential in order to completely eliminate viruses from a preparation. In regard to virus removal, given the fact that leukocyte removal and virus removal cannot be separately employed, replacing only the optical inactivation step of this reference for the membrane filtration step of LEE et al. or WO 01/14047 is inconceivable.

Secondly, HERMAN et al. describe that minimizing the loss of protein in plasma preparations is one of the merits of the virus removal by a photoreaction. However, membrane filtration is a method that causes such a loss. Referring to Example 1 of the present invention, for example, a decrease in the recovery of globulin and F-VIII with a large molecular weight after the filtration step using a virus-removing membrane cannot be denied, although no loss of albumin with a comparatively small molecular weight is observed. This is thought to be the result of insufficient permeation of large protein molecules having a size close to the pore size of the membrane and adsorption of such protein molecules to the membrane surface. Considering the fact that HERMAN et al. are concerned about protein loss, introducing the membrane filtration step of LEE et al. or WO 01/14047 is inconceivable.

Third, paying attention to the leukocyte-removal step, the leukocytes are removed in HERMAN et al. in order to remove viruses entrapped in the leukocytes as mentioned above. In LEE et al., when cellular components are mixed in the liquid, cells must be previously removed (column 6, lines 25-34). Although the reason is not clear, based on the fact that one of the applications of the method of LEE et al. is virus concentration for a gene therapy (column 4, lines 24-30), it is thought that unnecessary components are removed in order to increase the purity and qualities as a pharmaceutical preparation.

Further, WO 01/14047 fails to disclose or suggest leukocyte removal at all. WO 01/14047 describes that human blood is subjected to a plurality of purification processes such as Cohn fractionation and chromatography, after which the resulting human immunoglobulin is subjected to virus removal using a filter membrane. The product is considered to be a system not substantially containing cells such as leukocytes. In this manner, since viruses can be removed without specially removing leukocytes in WO 01/14047, it is quite natural that WO 01/14047 does not mention leukocyte removal.

On the other hand, the inventors of the present invention found that the fluid obtained from the whole blood after plasma separation contains components which cause a pressure increase in the later step. The inventors have then found that this problem can be solved by providing step (a) of reducing leukocytes from plasma separated from the whole blood before step (b).

As discussed above, none of the references of HERMAN et al., LEE et al. and WO 01/14047 describes or suggests the order of the step of reducing leukocytes from plasma which is separated from the whole blood followed by the step of filtering viruses, or the effect of suppressing pressure. A person having ordinary skill in the art would thus fail to produce a claimed embodiment of the present invention by combining these references. Considering the fact that HERMAN et al., which is a core of the

combination, does not allow separation of leukocyte removal and virus removal (inactivation by a photoreaction) and negates the membrane filtration, it is impossible to apply the references of LEE et al. and WO 01/14047 to HERMAN et al.

JP 3-146067 fails to address the above described deficiencies of HERMAN et al., LEE et al. and WO 01/14047.

A *prima facie* case of unpatentability has thus not been made.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Conclusion

The rejections have been overcome, obviated or rendered moot and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item:

- verified English translation of Japanese Appln. No. 2002-301433 filed on October 16, 2002